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Golgipathies in Neurodevelopment:

A New View of Old Defects

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Abstract

The Golgi Apparatus (GA) is involved in a whole spectrum of activities, from lipid biosynthesis and membrane secretion to the post-translational processing and trafficking of most proteins, to the control of mitosis, cell polarity, migration and morphogenesis, to diverse processes such as apoptosis, autophagy and the stress response. In keeping with its versatility, mutations in GA proteins lead to a number of different disorders, including syndromes with multi-system involvement. Intriguingly, however, over 40% of the GA-related genes known to be associated with disease affect the central or peripheral nervous system, highlighting the critical importance of the GA to neural function. We have previously proposed the term "Golgipathies" in relation to a group of disorders in which mutations in GA proteins or their molecular partners lead to consequences in terms of brain development, in particular postnatal-onset microcephaly (POM), white matter defects and intellectual disability (ID). Here, taking into account the broader role of the GA in the nervous system, we refine and enlarge this emerging concept to include other disorders whose symptoms may be indicative of altered neurodevelopmental processes, from neurogenesis to neuronal migration, to the secretory function critical for the maturation of postmitotic neurons and myelination.

Introduction

One hundred and twenty years ago, in 1898, Camillo Golgi first published his observations of an "internal reticular complex" that surrounded the nucleus of Purkinje cells in the barn owl cerebellum, using his now eponymous silver reduction method [1]. Despite Golgi's demonstration of his reticular complex is a variety of mammalian cell types in addition to neurons, the very existence of this complex, which we now call the Golgi complex or Golgi apparatus (GA), as an independent and consistent intracellular entity was in doubt for much of the first half of its history, in large part because of its variable morphology and technological and methodological limitations. Also in doubt was what specific role, if any, this strange structure could possibly play. We have known for a few decades now that the GA not only exists but is ubiquitous in all eukaryotic cells, from the yeast upward. However, our views on what it does and how it does it continue to evolve.

The best known and most widely accepted roles of the GA are of course in the biosynthesis of some lipids such as glycolipids and sphingomyelin, and in the processing, sorting, packing, routing and recycling of secretory cargo downstream of the endoplasmic reticulum (ER), roles that are important for cellular and organ function throughout the lifespan. However, the GA plays a number of other roles, many of which are of particular importance during development – it participates in cell division, migration, morphogenesis and growth (all of which involve diverse aspects including intracellular organization, polarity and compartmentalization), as well as apoptosis, autophagy and the stress response. In keeping with these multiple roles, many "GA proteins" are also present in other intracellular compartments and are involved in more than one function, including acting as signaling molecules, rather than acting at a purely structural/mechanical or enzymatic level.

The ubiquitous nature of the GA means that any pathogenic mutation perturbing the function of a GA protein could and mostly does result in clinical repercussions across multiple tissues and systems. Strikingly, of the mutated GA-associated genes identified in various monogenic disorders so far, over 40% affect the normal development or functioning of the central or peripheral nervous system, a far greater proportion than for any other tissue type [2], highlighting its crucial roles in different types of neural cells. Indeed, the magnitude of this impact on the nervous system structure and physiology and on neurodevelopment in particular should not be surprising, when one considers the intensive use that neurons and glia presumably make of the GA – in the intricately coordinated processes involved in progenitor cell organization, orientation and mitosis; the subsequent highly directional migration of young neurons to their target regions; the exponential increase in surface area and thus of the biosynthesis of both membrane lipids and proteins required by diverse processes such as dendritic arborization in neurons and myelin sheath production in oligodendrocytes; the heavy demands of synaptogenesis and synaptic and neurosecretory activity, etc. The existence of Golgi outposts in dendrites is a prime example of the adaptation of the GA to the highly compartmentalized nature of the nervous system and its specific trafficking needs (reviewed in [3,4]).

Intriguingly, during the course of our identification of the causal gene and molecular mechanisms underlying Dyggve-Melchior-Clausen (DMC, MIM #223800) syndrome, a disorder in which skeletal defects are associated with a characteristic neurological profile combining postnatal-onset microcephaly (POM), white matter deficits and intellectual disability (ID) [5], we noted the presence of the same combination of symptoms in several other monogenic disorders, each of which was linked to a defect in a gene involved in the GA trafficking machinery. This common profile indicated a similar pathophysiology – defective

neuronal or oligodendrocytic maturation at the post-mitotic stage, thus leading to symptoms later during neurodevelopment than in the primary or congenital microcephalies, which result principally from proliferation deficits. Additionally, several of these newly or previously identified disorders appeared to involve a mutation in a GA-associated member of the small RAB GTPase family, which are involved in a plethora of trafficking functions in the cell, or in molecules that interact with the RABs, including their direct effectors and modulators such as the guanine nucleotide exchange factors – GEFs – which activate them by replacing GDP by GTP and allowing them to bind specific effectors, or the GTPase activating proteins – GAPs, which dissociate the active complex. These observations prompted us to propose the term "Golgipathies" or "Golgipathic microcephalies" to designate this emerging class of disorders characterized by a similar phenotype (POM, white matter deficits, notably an abnormal corpus callosum, and varying degrees of cognitive impairment), and caused by mutations in RAB GTPases or their molecular partners [4]. However, an examination of the literature and recently published studies provides ample evidence that defective GA proteins and processes are linked to a wide spectrum of neurodevelopmental defects in addition to the combination that first drew our attention. Not only are there a large number of isolated reports of POM related to GA- or RAB-associated mutations, but a number of other disorders, including several characterized by congenital microcephaly, could also justifiably be classified as Golgipathies, based on the fact that the primary pathogenic mechanism in all of them is a defective GA protein, regardless of its intracellular function (GA structure or intracellular organization, trafficking machinery in the anterograde or retrograde directions, post-translational modifications, cell-cycle involvement…). In light of these new insights, we would like to refine the notion of Golgipathies, taking into account their major neurodevelopmental involvement, with a brief discussion of the relationship between these disorders and the possible GA functions affected.

Golgipathies: more microcephalies and more than microcephalies

Despite their great variety, Golgipathies with a neurodevelopmental component also show considerable overlap and a number of unifying features. Some of these putative neurodevelopmental Golgipathies are described below, grouped according to their principal clinical signs (presence or absence of microcephaly and its onset), and the probable function or position in the trafficking pathway of the affected protein, in order to stimulate discussion as to their potential classification. We have excluded cancer-related GA genes/proteins or those involved in primarily neurodegenerative processes.

I. POM Golgipathies related to RAB GTPases and their molecular partners:

Perhaps due to the fact that most important and "permanent" functions of the GA is that of lipid and protein trafficking, crucial throughout the lifespan of the cell, the POMs constitute a disproportionately large group of Golgipathies affecting neurodevelopment. While many involve other organs and tissues and show remarkable differences in phenotype between one individual and the next, for the purposes of this review, we will concentrate on the neurological aspects (summarized in **Table 1**).

Dyggve-Melchior-Clausen syndrome (DMC; MIM #223800), which first prompted our speculation about Golgipathies as a class of disorders, is an autosomal recessive skeletal dysplasia associated with POM and ID, and caused by loss-of-function mutations in the *DYM* gene encoding DYMECLIN, a GA protein involved in intracellular trafficking [6-8]. Brain MRI reveals a marked thinning of the corpus callosum and brain stem, supported by significant deficits in the volume and structure of myelin in Dym-/- mutant mice [5] Dym-deficient neurons display a fragmented GA and impaired ER-to-GA trafficking [5], but Dym may also

play a role in the retrograde transport of vesicles from the GA to the ER [7]. Several lines of evidence suggest that it has a tethering role during vesicle trafficking between the ER and the GA [6,7] in conjunction with the golgin GIANTIN and interactions with RAB1 or RAB6, the most abundant type of RAB [9-11]. Interestingly, *Smith McCort dysplasia*, a clinical variant of DMC syndrome with identical skeletal defects but normal intelligence and no microcephaly, has been found to result either from specific missense mutations in *DYM* that could result in some residual activity of the protein (SMC1; MIM #607326) [6,12] or from loss-of-function mutations in the RAB33B GTPase, also localized in the GA (SMC2; MIM #615222) [13,14].

Warburg-Micro syndrome (WARBM1-4; MIM #600118, #614225, #614222, #615663) is an autosomal recessive disorder [15] characterized by neurodevelopmental defects including POM with profound ID, and progressive limb spasticity associated with progressive peripheral axonal neuropathy [16], severe visual impairment and hypogonadism. Brain MRI shows bilateral frontal polymicrogyria and hypoplasia of the corpus callosum and cerebellar vermis [17,18]. Loss-of-function mutations in four distinct genes, *RAB3GAP1*, *RAB3GAP2*, *RAB18* and *TBC1D20*, have been implicated in WARBM [18-20]. RAB18 has recently been confirmed to localize in the ER and the *cis*-Golgi compartment [21], in addition to other compartments. While TBC1D20 acts as a GAP for RAB18, in addition to acting on ER-localized RAB1 [22] the RAB3GAP complex in this context acts not as a GAP but as a GEF for RAB18 [23]. In the related *Martsolf syndrome* (MIM #212720), only *RAB3GAP2* mutations have been identified, but most patients also display severe neurodevelopmental defects including POM and white matter defects (where examined), ID, hypogonadism and ocular defects [19,24,25].

Mutations in *COL4A3BP* (collagen 4A3 binding protein, also known as Goodpasture antigen binding protein, GPBP, or ceramide transporter, CERT) lead to an *autosomal dominant mental retardation* (MRD34; MIM #616351). The COL4A3BP protein is thought to mediate ER-to-GA transport of ceramide, an essential lipid component. One of the first patients

identified with a mutation in this gene presented with POM in addition to other neurological and skeletal defects [26].

Autosomal recessive mental retardation 13 (MRT13; MIM #613192) is linked to loss-of-function mutations in *TRAPPC9*. Initially considered a nonsyndromic autosomal recessive ID [27-29], with additional cases, MRT13 is beginning to show a fairly distinctive phenotype, including moderate to severe POM, a peculiar facial appearance, obesity and hypotonia. MRI reveals a reduction in cerebral white matter with a marked thinning of the corpus callosum [30-32]. TRAPPC9 is a subunit of the Trafficking Protein Particle (TRAPP) complex that mediates the tethering of COPII-coated ER-derived vesicles to *cis*-Golgi membranes [33]. The TRAPP complex acts by activating RAB1, which in turn recruits specific *cis*-Golgi effectors such as the golgins P115 and GM130 to allow vesicle tethering [34]. The TRAPP complex and TRAPPC9 in particular are also involved in the interaction between COPII-coated vesicles and the microtubule motor protein dynactin 1 (DCTN1, equivalent to the Drosophila $p150^{Glued}$) [35].

Progressive childhood encephalopathy (PEBAS; MIM #617669), also linked to mutations in a TRAPP subunit, TRAPPC12, has been identified in 2 families as being linked to progressive microcephaly (including one case of POM), agenesis of the corpus callosum and other MRI abnormalities, and severe developmental delays [36]. Mutations in another TRAPP subunit, TRAPPC6B, have also been linked to a *POM syndrome* (NEDMEBA; MIM #617862) in several families in a recent report [37].

In *Takenouchi-Kosaki syndrome* (TKS; MIM #616737), caused by mutations in the GA GTPase CDC42, which regulates bidirectional Golgi transport by regulating the cargo sorting and carrier formation functions of COPI [38], affected patients show a range of phenotypes affecting different organs, including ID and either POM or congenital microcephaly (reviewed in [39]).

A neuromuscular syndrome with microcephaly noticeable from the 4th postnatal month has been described in an individual who also displayed developmental delays, seizures, hypotonia and muscular dystrophy [40]. Brain MRI revealed delayed myelination and a thinning of the corpus callosum. The molecular cause was a loss of function of the *GOLGA2* gene (MIM #602582), which encodes GM130, a multifunctional golgin involved in both the assembly/maintenance of GA structure and the regulation of the secretory pathway and vesicle tethering to the *cis*-Golgi compartment through interactions with RAB1B, P115 etc.; GM130 also binds to other RAB proteins involved in membrane traffic regulation at the ER/Golgi interface, such as RAB2 and RAB33B [41-43].

Autosomal recessive mental retardation 61 (MRT61; MIM #617773), also called Alwadei syndrome, is a POM syndrome that includes profound ID, epilepsy in two cases and a thin corpus callosum [44]; it has been found to be caused by mutations in IPORIN (MIM #617773), a protein encoded by the *RUSC2* gene. Little is known about the RUSC2 protein except that it is ubiquitous and highly expressed in the brain, and interacts with both RAB1B and possibly directly with GM130 [45].

Cohen syndrome (COH; #MIM 216550) is an autosomal recessive disorder characterized by motor delays, progressive retinal dystrophy and severe myopia, hypotonia, joint hypermobility and progressive POM associated with ID [46], associated at times with non-neurological signs [47]. Brain MRI reveals a relatively thicker but more compact corpus callosum in some patients, associated with markedly smaller sagittal diameters of the brain stem [48]. *COH1*, the only gene associated with Cohen syndrome so far, encodes the vacuolar protein-sorting protein VPS13B, a large peripheral membrane protein that is actively recruited at the GA by RAB6 [49,50]. VPS13B likely plays a specific role in the dynamics and function of the GA, in particular during neuronal maturation.

Progressive Cerebello-Cerebral Atrophy type 2 or Ponto-Cerebellar Hypoplasia type 2E (PCCA2/PCH2E; MIM #615851) is an autosomal recessive neurodegenerative disorder characterized by normal development during the initial months of life, followed by motor delays, progressive POM, progressive spasticity and epileptic seizures by two years of age [51]. Brain MRI reveals a gradual decrease in cerebral white matter associated with delayed myelination and thinning of the corpus callosum [51]. The responsible gene encodes VPS53, another vacuolar protein-sorting protein that participates in the transport and recycling of endosome-derived transport vesicles [52]. VPS53 is part of two large multisubunit complexes named Golgi-associated retrograde protein (GARP) and Endosome-associated recycling protein (EARP), that ensure the proper tethering between endosomes and their acceptor compartment [53,54]. Both complexes cooperate with SNAREs for subsequent membrane fusion. GARP has been found to interact with RAB6A at the TGN [55] and EARP associates with RAB4-containing vesicles [54]. A *previously unknown neurodevelopmental disorder* linked to a mutation in yet another GARP/EARP subunit, VPS51, also appears to exist, based on our own observations (case report in preparation) as well as a BioRxive description of a 6-year-old patient with severe global developmental delay, pontocerebellar abnormalities, microcephaly, hypotonia, epilepsy and several systemic and peripheral dysfunctions (BioRxiv 409441, 2018).

A pontocerebellar hypoplasia caused by TBC1D23 mutations (PCH11; MIM #617695) has been shown in two different reports to be associated with POM or microcephaly of unknown onset, along with various other neurodevelopmental deficits and neurological signs (including a hypoplastic corpus callosum, as seen in several Golgipathic POMs, severe cognitive delays, motor weakness or lack of motricity, behavioral problems etc.) [56,57]. TBC1D23, like TBC1D20 in Warburg-Micro syndrome, appears to be a RAB GAP (although neither its GTPase activity nor its RAB specificity has been clearly evidenced so far). It is localized at the *trans*-Golgi and regulated by the small GTPases ARL1 and ARL8, and appears to mediate the binding of endosomal vesicles to golgin-245 and golgin-97 on *trans*-Golgi

membranes to mediate retrograde transport [58]. It has been implicated in the regulation of neuronal migration/positioning during corticogenesis, as well as neurite/axon differentiation [56].

Autosomal recessive periventricular heterotopia with microcephaly (ARPHM; MIM #608097*)* has been described in several patients to be caused by *ARFGEF2* mutations. The microcephaly in these reports is progressive postnatally in three reports [59-61] and of unknown onset/progression in one [62]. The patients also display severe developmental delays and ID, epilepsy, brain atrophy and myelination delays associated with a thin corpus callosum. *ARFGEF2* encodes BIG2, a GA protein responsible for interior membrane trafficking in the *trans*-Golgi network and endosomes [63]. BIG2 interacts with RAB11, a *trans*-Golgi protein involved in diverse functions such as synaptic transmission, but also neuronal migration and axonal growth, functions that could explain the phenotypes seen in the reports above [64,65].

MEDNIK syndrome (MEDNIK; MIM #609313) is caused by mutations in *AP1S1*, a subunit of one of the five adaptor protein complexes (AP1-5), located at the *trans*-Golgi and in endosomes, that match cargo molecules, including neurotransmitters (and in the case of AP1S1, specifically, the copper pumps ATP7A and B) to their carriers (reviewed in [66]). Symptoms of MEDNIK syndrome, although predominantly cutaneous, include POM in addition to other typical neurological signs such as moderate to severe ID and deafness [67]. Montpetit and colleagues also mention the occurrence of peripheral neuropathy and microcephaly in the original French-Canadian cohort, without indicating age of onset, when discussing their animal model [68], although the original article by Saba and colleagues and subsequent discussions of this cohort only mention brain "atrophy" [67-69]. In addition, mutations in *AP1S2* cause *Pettigrew syndrome* (PGS, MIM #304340), an X-linked disorder characterized by ID, seizures, Dandy-Walker malformation and microcephaly, possibly postnatal, although head circumference was variable in the original family [70,71].

COG-associated Congenital Disorders of Glycosylation (CDGs) represent one subgroup of a very large family of multisystemic autosomal recessive pathologies involving dysfunctions in the processing of N- and O-linked glycans. While most of the mutations identified so far involve genes encoding glycosylation enzymes [72], the CDGs described in this paragraph are caused by defects in one of the 8 subunits of the Conserved Oligomeric Golgi (COG) complex, localized to the *cis*- and medial-Golgi as well as surrounding vesicles [73]. The COG complex is thought to act as a tethering factor, in particular during intra-GA and retrograde GA-to-ER trafficking, where it mediates the recycling of glycosyltransferases [74], suggesting that the incidence of CDG when COG subunits are mutated is likely due to the inability of these glycosylation enzymes to reach their target proteins [73]. COG-associated CDGs are associated with multiple neurological manifestations, including POM in patients carrying mutations in *COG1* (MIM #611209), *COG2* (MIM #617395), *COG4* (MIM #613489), *COG5* (MIM #613612), *COG7* (MIM #608779) and *COG8* (MIM #611182) [75-81]. Brain MRI has revealed hypoplasia of the corpus callosum in four patients [77,78] and brainstem atrophy in one case [75]. *COG6* mutations have also been associated with borderline POM in Shaheen syndrome (SHNS; MIM #615328) as well as a CDG with congenital microcephaly (MIM #614576) [82,83]. Interestingly, the COG complex has been shown to interact with molecules at all levels of GA organization and trafficking as well as a number of GA-associated RABs (see [4] for an overview).

Another family of GA-associated proteins whose mutation gives rise to a wide range of CDGs with neurological phenotypes is the solute carrier family 35 (SLC35), whose members carry a variety of molecules, mostly sugars, to the GA for the glycosylation of proteins. Mutations in SLC35A3 have been associated with POM and ID [84] in a syndrome characterized by *arthrogryposis, mental retardation and seizures* (AMRS; MIM #615553). Similarly, mutations in SLC35C1 give rise to *CDG2C* (MIM #266265), in which severe ID and POM have also been noted [85], while mutations in other family members give rise to various

CDGs with ID, microcephaly of unknown onset, and other neurological manifestations (e.g. SLC35A1: CDG2F, MIM #603585; SLC35A2: CDG2M, MIM #300896).

Among CDGs caused by a defective trafficking mechanism, rather than an enzymatic or metabolic deficiency, and including POM, psychomotor delays and white matter abnormalities among their clinical signs, should be included *CDG2K*, caused by mutations in the transmembrane GA protein TMEM165 (MIM #614727). While the exact function of this protein is not yet known, it is probably an ion transporter that plays a role in pH, calcium or manganese homeostasis, and mutations also appear to affect GA morphology [86,87].

II. Other microcephalies or macrocephalies related to impaired GA function

A number of other reports of patients with microcephalies linked to mutations in GA-associated proteins exist in the literature. However, data on whether these microcephalies are congenital or postnatal (or congenital but progressive after birth) is not always available. Further studies might well turn up other syndromes where a POM or a progressive worsening of microcephaly would indicate a defect in maturation (including trafficking or biosynthetic defects) or other processes that take place later in development, such as gliogenesis, as opposed to a congenital microcephaly that would indicate a deficit in the production of new neurons earlier in development, even though these different microcephalies are likely to lie along the same continuum rather than being mutually exclusive. The other side of the coin is that mutations in several GA-related proteins appear to result in macrocephaly, possibly indicating an opposite effect on the regulation of neurogenesis or neuronal apoptosis during maturation. A few examples of these other microcephalies and macrocephalies linked to GA protein mutations are given below (summarized in **Table 2**).

Mutations in the *WDR62* gene, which codes for a WD40 repeat protein highly expressed in the developing brain, cause *autosomal recessive primary microcephaly 2* (MCPH2; MIM #604317) with seizures and ID in addition to congenital microcephaly [88,89]. Interestingly, even though it is best known for its presence at the centrosome during mitosis and appears to play a critical role in neuronal progenitor proliferation during corticogenesis, WDR62 also associates with GM130 and is localized at the GA during interphase, where its function is unknown [89]. Similarly, at least two other *MCPH* genes encode products that associate with the GA. *Autosomal recessive primary microcephaly 3* (MCPH3; MIM #604804) is related to mutations in the CDK5 regulatory subunit-associated protein 2, CDK5RAP2 [90], which plays an important role in progenitor division during neurogenesis [91,92]. Interestingly, CKD5RAP2 is necessary for microtubule nucleation and organization not only at the centrosome but also at the GA [93,94]. Similarly, we and others have found that *autosomal recessive primary microcephaly 17* (MCPH17; MIM #617090) is caused by mutations in the gene for the Citron Rho-interacting serine/threonine kinase, CIT [95,96]. The longer CIT-K protein, which localizes at the cleavage furrow and midbody during cell division (reviewed in [97]), is known from animal models to play a role in cytokinesis and progenitor survival during neurogenesis [98], while the shorter brain-specific isoform, CIT-N, is known to be enriched at the somatic GA of certain neurons as well as in dendrites where it interacts with peripheral Golgi outposts and plays a key role in the maintenance of dendritic spines [99,100].

Mutations in TRAPPC11, a subunit of the TRAPP complex that plays a role in ER-GA trafficking and activates several RABs, as described above, lead to a *limb girdle muscular dystrophy* (LGMDR18; MIM #615356) with microcephaly of unknown onset, myopathy, infantile hyperkinetic movements, ataxia, and ID [101,102].

A microcephalic dwarfism syndrome (SRMMD; MIM #617164) characterized by, in addition to microcephaly, facial dysmorphism, severe micrognathia, rhizomelic shortening and

mild developmental delay has been associated with heterozygous mutations in *ARCN1* [103]. *ARCN1* (*COPD*) encodes Archain 1, the delta subunit of the vesicular coat protein COPI, necessary for both intra-GA and GA-ER retrograde transport, and ARCN1 haploinsufficiency leads to COPI-mediated transport defects. In addition, a hypomorphic missense mutation in the *COPB2* gene, encoding the beta subunit of COPI, has also recently been found to be the cause of a primary autosomal recessive microcephaly (MCPH19; MIM #617800) in which the congenital microcephaly is associated with severe developmental delay, cortical blindness and spasticity [104]. COPB2 appears to be involved not only in retrograde GA-ER transport, possibly interacting with DYMECLIN [7], but in early neuronal proliferation and apoptosis [104].

A PEHO (progressive encephalopathy with edema, hypsarrhythmia and optic atrophy) -like syndrome (PEHOL; MIM #617507) caused by a mutation in the *CCDC88A* gene coding for GIRDIN, a coiled-coil GA protein, shows, in addition to profound psychomotor delay, seizures and progressive brain atrophy, severe congenital microcephaly in all patients, and dysmyelination in one case [105]. GIRDIN, also known as KIAA1212, appears to be involved in the migration and positioning of new neurons, controlling soma size and dendritic branching [106].

AP4-deficiency syndrome is caused by a mutation in a subunit of another of the five adaptor protein complexes, AP1-5, mentioned above (reviewed in [66]). AP4-deficiency syndrome, which includes a very large range of phenotypes, may be included among the large number of hereditary spastic paraplegias [107]. Among them, *AP4E1* mutations (MIM #613744) lead to a form of hereditary spastic paraplegia with congenital microcephaly, ID, thin corpus callosum, psychomotor deficits and spasticity [108-110], which Moreno-de-Luca and colleagues found to be similar to another hereditary spastic paraplegia caused by mutations in *AP4M1* (MIM #612936), in which several patients displayed microcephaly in addition to other

neurological signs [111]. Similarly, Abou Jamra and colleagues also found microcephaly, along with a variety of other symptoms in patients with *AP4B1* (MIM #614066) and *AP4S1* mutations (MIM #614067) [108]. Surprisingly, microcephaly of unknown onset associated with ID has also been noted in *Hermansky-Pudlak syndrome 2* (HPS2; MIM #608233), not commonly thought to be associated with neurodevelopment; in this disorder, mutations in *AP3B1* principally lead to oculocutaneous albinism, immunodeficiency and hematological abnormalities [112].

As in the case of the TRAPP and AP protein families, mutations in another SLC family member, SLC9A6, are also associated with other forms of microcephaly (congenital, progressive, or of unknown onset) and severe ID in the X-linked mental retardation known as *Christianson syndrome* (MRXSCH; MIM #300243) [113-115].

In an early infantile epileptic encephalopathy (EIEE49, MIM #617281) caused by mutations in *DENND5A*, a gene encoding a GA-localized GTPase activator thought to play a role in neuronal differentiation, almost all affected individuals show microcephaly in addition to various other neurological signs, including seizure onset in the neonatal period, global developmental delay with ID and lack of speech, hypotonia, spasticity etc. [116,117]. DENND5A acts as a GEF for the neuronal GA-specific GTPase RAB39 [118], which is involved in regulating the number and morphology of neurite growth cones and in synapse formation and maintenance, including alpha-synuclein homeostasis. However, deficits in RAB39B are also associated with an *X-linked form of ID* with macrocephaly rather than microcephaly (MRX72; MIM #300271) [119,120]. Macrocephaly is also a feature of RAB39B-associated early-onset Parkinsonism or *Waisman syndrome* (WSMN; MIM #311510) [121,122].

Mutations in another GTPase activator, HERC1, which is localized to the cytoplasm and GA/vesicular compartments and acts as a GEF for ARF1, and possibly RAB3A and RAB5

[123], also result in a *macrocephaly syndrome with dysmorphic facies and psychomotor retardation* (MDFPMR; MIM #617011) [124-126].

Similarly, in *autosomal dominant mental retardation 48* (MRD48; MIM #617751) mutations in the gene encoding the small Rho GTPase RAC1, which appears to interact with various GA proteins and to play a distinct role in neuronal progenitor proliferation, lead to ID with either microcephaly or macrocephaly, as well as a developmental delay, seizures, absent speech and a number of defects on MRI [127]. Interestingly, *SPATA13* (also known as *ASEF2*), encoding a GEF for both RAC1 and CDC42 (involved in Takenouchi-Kosaki syndrome, as mentioned above) that is enriched in the prenatal frontal cortex and plays a role in dendritic spine formation and cell migration, possibly by regulating actin cytoskeletal remodeling [128,129], is among a set of 26 newly identified ID genes [130].

Another GA-associated gene implicated in corticogenesis is the gene for the pseudokinase STRADA (also known as STE20 related kinase adaptor alpha, or LYK5), deletions in which give rise to macrocephaly in a syndrome encompassing *polyhydramnios, megalencephaly and symptomatic epilepsy* (PMSE; MIM #611087) [131,132]. STRADA appears to form a complex with STK25 and the golgin GM130 to regulate GA morphology and positioning, thus controlling neuronal differentiation and integration during development [133].

III. GA protein mutations associated with other neurodevelopmental anomalies

Not all GA proteins appear to be associated with microcephalic or macrocephalic syndromes when mutated. However, a number of GA proteins do have other significantly neurodevelopmental effects involving either the central or peripheral nervous system, and lead to phenotypes that include ID, ataxias, peripheral neuropathies or sensorineural loss. Some of these are described below, and also summarized in **Table 3** (excluding GA-localized enzymes

whose role lies primarily in protein or lipid biosynthesis/modification, and that are thus likely to have metabolic effects rather than mechanistic ones).

Many GA proteins other than those described in Sections I and II above are implicated in various forms of ID, even without being associated with microcephaly or macrocephaly. For example, mutations in the RAB-GDP dissociation inhibitor GDI1 are responsible for a non-syndromic X-linked form of ID (MRX41/MRX48; MIM #300849) [134-136].

A non-RAB molecular partner of BIG2 (*ARFGEF2*), which, as we have discussed above, causes a periventricular heterotopia and progressive microcephaly, is another GA protein, FILAMIN alpha (FLNA), that plays a role in neuronal migration by regulating the relocalization of BIG2 and the activation of ARF1 at the cell membrane [137]. Mutations in *FLNA* lead to X-linked periventricular nodular heterotopia (PVNH1; MIM #300049), characterized by brain structural abnormalities and ID, at least in males, but with no known microcephaly (reviewed in [138]).

Mutations in the gene for phosphofurin acidic cluster sorting protein, PACS1, a *trans*-Golgi protein involved in the trafficking of FURIN, lead to *Schuurs-Hoeijmakers syndrome*, an autosomal dominant mental retardation (MRD17; MIM #615009), characterized by ID, dysmorphic features, and brain MRI defects in addition to skeletal defects [139].

Similarly, autosomal recessive mutations in *SCYL1*, which encodes a protein located at the interface between the GA and COPI-coated vesicles and likely involved in trafficking functions, lead to another form of autosomal recessive *spinocerebellar ataxia* (SCAR21; MIM #616719), characterized by cerebellar atrophy, peripheral neuropathy and mild ID [140].

Several mutations in the *BICD2* gene, which encodes the golgin BICAUDAL2 that interacts with the dynein-dynactin motor complex and RAB6A, have been shown to cause an *autosomal dominant form of spinal muscular atrophy* (SMALED2; MIM #615290) [141-143].

Similarly, mutations in *KIF1C*, a kinesin family motor protein that interacts with RAB6 to mediate GA tethering [144], lead to an autosomal recessive form of hereditary spastic paraplegia, *spastic ataxia 2* (SPAX2; MIM #611302) [145-147].

Mutations in the *TANGO2* gene, which encodes a protein thought to be involved in loading cargo into vesicles at the ER but is also localized at the GA, lead to a complex syndrome characterized by *metabolic encephalomyopathic crises, recurrent, with rhabdomyolysis, cardiac arrhythmias, and neurodegeneration* (MECRCN; MIM #616878), with multiple neurodevelopmental manifestations including seizures and ataxia [148,149].

Mutations in GOSR2, a GA SNARE complex member, lead to early-onset ataxia and *progressive myoclonic epilepsy* (EPM6; MIM #614018) in childhood and skeletal deformities by adolescence [150,151].

A *cis*-Golgi protein encoded by *RETREG1* or *FAM134B* has been found to be mutated in *hereditary sensory and autonomic neuropathy type IIB* (HSAN2B; MIM #613115), characterized by childhood onset autonomic neuropathy, and heavily impaired sensory and sometimes motor function [152].

Among the GA-associated genes involved in sensorineural loss, *OSBPL2*, which encodes a fatty-acid receptor, oxysterol binding protein-like protein 2, is mutated in a *nonsyndromic autosomal dominant form of deafness* with childhood onset (DFNA67; MIM #616340) [153,154]. In *Hermansky-Pudlak syndrome 1* (HPS1, MIM #203300), a syndrome usually characterized in humans by albinism and excessive bleeding, as in HPS2 (discussed in Section II), mutations in the AP3D1 adaptor complex subunit give rise to a phenotype hearing loss in addition to neurodevelopmental delay and generalized seizures (HSP10; MIM #617050) [155]. Several of the genes and syndromes described above also have an impact on vision (several AP and COG subunits, RAB3GAP2, and TBC1D20, to name a few).

Sometimes, mutations in GA genes that are not thought to be associated with neurological symptoms might in fact have unnoticed neurodevelopmental effects, as in the case of the Hermansky-Pudlak syndromes, as seen above. In other cases, disorders considered to be neurodegenerative might have a neurodevelopmental component in rare early onset forms, such as some spinocerebellar ataxias: type 2 (MIM #183090, *ATXN2),* type 5 and 14 (MIM #600224; MIM #615386, *SPTBN2*) and type 8 (MIM #610743, *SYNE1*) [156].

The GA also plays an essential role in the biosynthesis or modification of the cargo being transported. While these are generally considered to be "metabolic" disorders and are related more to the modification of trafficked molecules than to trafficking per se, mutations in many of these also have neurodevelopmental consequences (for a brief overview, see [72]). For instance, it is the site of synthesis of some glycolipids and sphingomyelin, a major component of myelin and essential for normal morphogenesis or plasticity of membrane-rich cell types such as neurons (during migration, rapid axonal growth or dendritic arborization etc.) or oligodendrocytes (for the generation of the myelin sheath), from lipid precursors synthesized in the ER (glycerol phospholipids, cholesterol and ceramide). Mutations in genes involved in lipid biosynthesis and processing have also been associated with several neurodevelopmental defects. For example, a mutation in *ACER3*, encoding an ER and Golgi ceramidase involved in sphingolipid metabolism, has been identified in a family with progressive impairment and regression of neurodevelopment during the first year of life, leukodystrophy-like signs and peripheral neuropathy (PLDECO, MIM #617762) [157]. Another GA gene involved in lipid metabolism and that leads to neurodevelopmental deficits is that encoding DDHD domain containing 2 (DDHD2), a phospholipase with a major role in brain triglyceride metabolism [158], mutations in which result in hereditary spastic paraplegia type 54 (SPG54, MIM #615033) [159]. Mutations in the *PGAP2* and *PGAP3* genes (post-GPI attachment to proteins 2 and 3), which are essential for the glycolipid remodeling of GPI anchor proteins, have been associated with developmental delays and ID, in addition to microcephaly in several families

(HPMRS3, MIM #614207 and HPMRS4, MIM #615716) [160-164], while *PGAP1* has also been linked to ID [165,166].

Among the cargo-modifying enzymes present in the GA are a very large complement of different glycosyltransferases and glycosidases, in addition to enzymes responsible for adding or removing phosphate, sulphate, lipid and other groups from proteins. To give a few examples, mutations in the acetylglucosaminyltransferase gene *MGAT2*, a member of the N-glycosylation pathway, lead to CDG type IIa (CDG2A, MIM #212066), characterized by seizures, developmental delays and ID in addition to other symptoms [167]. Another member of the N-glycosylation pathway is β1,4 galactosyltransferase I, implicated in severe forms of CDG-IId (CDG2D, MIM #607091) with neurological deficits, hydrocephalus, myopathy and defective blood clotting [168]. CDG type II is also caused by mutations in the mannosidase gene *MAN1B1*, which lead to a syndrome characterized by ID and truncal obesity, while *INPP5E* (inositol polyphosphate-5-phosphatase E) mutations have been implicated in the neurodevelopmental disorders Joubert (JBTS1, MIM #213300) and MORM syndromes (MORMS, MIM #610156) [169,170], the latter of which also includes ID and truncal obesity. Several types of muscular dystrophy with neurological involvement are also caused by defects in GA glycosylation genes (e.g. FKRP, LARGE, POMGnT1). Similarly, a variety of members of the solute carrier families (SLC), which transport various metabolites (sugars, acetylCoA, zinc…) are involved in CDGs and other neurodevelopmental disorders including spastic paraplegias, ID, epilepsy etc [2].

Another GA protein family is that of the copper-transporting P-type ATPases, ATP7A and B (reviewed in [171]), which are specifically trafficked by AP1S1, whose mutation causes MEDNIK syndrome (mentioned in Section I above). Under basal conditions, ATP7A and B, which are ion pumps, are located in the *trans*-Golgi network (TGN) and translocates copper across intracellular membranes into the secretory pathway for incorporation into copper-

dependent enzymes. Their mutation, while having multisystemic consequences due to copper deposition in the liver and skin, for example, in addition to the brain, has been linked to Menkes disease (MNK, MIM #309400) or occipital horn syndrome (OHS, MIM #304150), or spinal muscular atrophy (SMAX3, MIM #300489) (ATP7A), all disorders with a childhood onset, or dystonia and neurodegeneration of either childhood or late onset (ATP7B).

The link between Golgipathies, GA function and neurodevelopment

What is the explanation for the exceptionally large spectrum of diseases and symptoms associated with defective GA proteins above, even when one limits the discussion to those with neurodevelopmental consequences?

The GA is not only involved in but lies at the crossroads of a number of distinct and crucial cellular processes, some of which have only recently begun to be elucidated. In addition, individual GA proteins themselves often participate in more than one function or pathway, depending on the cellular context, developmental stage and the pathophysiological state, and some proteins, such as the small RAB GTPases, belong to extended families with a whole gamut of functions, both within and outside the GA. However, much is still unknown regarding the precise functions and the molecular partners of the great majority of GA proteins, and existing information often comes from lower species or organs outside the nervous system. Despite these overlaps and restrictions, obtaining even an incomplete understanding of some of these functions and proteins may provide insights into the complex repercussions of their mutation or deregulation, including the various neurodevelopmental processes impacted. **Figure 1** illustrates the relationship between some of the principal GA functions and the different stages of neurodevelopment in which they are implicated, taking the central nervous system as an example. Understanding these functions and how they evolve over the lifespan of the cell and the organism would also help elucidate the reason why mutations in some families

of GA proteins appear to cause a spectrum of deficits rather than discrete phenotypic entities (e.g. both congenital microcephalies and POM in the case of defective TRAPP, AP or SLC complex subunits).

Maintenance of GA structure, integrity and position:

A distinctive characteristic of the GA in the cells of mammals and other vertebrates is its structure – it is made up of stacks of flattened cisternae, as in protists, plants and invertebrates, but these stacks are linked to each other to form a "ribbon" [172,173]. Cisternal stacking is necessary for normal trafficking, while the ribbon structure is thought to play a role in higher order functions such as mitosis and apoptosis, cell polarity/migration and stress responses (reviewed in [174,175]). A number of GA proteins are involved in regulating this typical structure and the integrity of the GA. Prominent among these are various members of the coiled-coil golgin family of proteins (e.g. GM130, GIANTIN, P115, GOLGIN-45, GMAP210, GIRDIN etc.), many of which interact with coiled-coil GRASP proteins and small GTPases or GTP-binding proteins of the RAB, ARF and ARL families to control cisternal structure and stacking in the GA. (reviewed in [174-176]). Many of the GA-associated GTPases are in turn regulated by families of regulatory proteins, such as the GEFs and GAPs, which act at various points and target effector molecules in the trafficking pathway. Among the GA-associated members of these large families of proteins, some are specifically expressed in neural tissue, for example RAB6B [177] and to some extent RAB6C [178]. Several golgins (e.g. Bicaudal D and GMAP210) and RAB GTPases (for instance, the multifunctional RAB6) are involved in interactions between the GA and the microtubule cytoskeleton, including molecular motors such as DYNEIN, and help in the organization of the GA ribbon by recruiting GA stacks to the microtubule organizing center (MTOC). Some, such as GM130, through their interactions with other polarity-determining kinases as well as their role in microtubule nucleation and organization [179-182], dictate the polarity of the GA and thus of

the cell or neuron as a whole [183], thus controlling its correct differentiation and function. The fragmentation of the GA ribbon through the phosphorylation of the GRASPs and other molecules might also allow GA repositioning and thus migration, growth or differentiation [184] (fragmentation is also essential for the progression of the cell cycle, discussed below). In addition to structural changes, GM130 and GRASP65 also form part of signaling cascades that regulate cell migration [181].

Secretory and membrane trafficking:

GA structure and integrity and many of the large array of molecules that control them are also essential for the various steps involved in vesicular transport – coat components and adaptors that control vesicle targeting and recognition, the coiled-coil golgins necessary for their capture and the SNAREs and COGs that help in tethering and fusion, RAB and other small GTPases that mediate the choreographed attachment and detachment of molecules at each step, adaptors, activators and inhibitors for each of the above etc. Interfering with these proteins or their interactions results in disrupted GA structure/organization and abnormal protein and lipid transport (see for example the effects of disrupting various RABs on GA structure, reviewed in [185]), important for both neuronal and oligodendrocyte function, including the rapid membrane expansion needed for the establishment of neuronal outgrowth and connectivity and myelination. Mutations in these genes are involved in a number of Golgipathies with diverse symptoms, including the large majority of the POM syndromes with white matter defects that we have listed above (Dyggve-Melchior-Clausen syndrome, Warburg-Micro and Martsolf Syndromes, Cohen Syndrome Progressive Cerebello-Cerebral Atrophy Type 2 and other Pontocerebellar Hypoplasias, microcephalies related to mutations in the TRAPP complex and COG-related CDGs, to name a few) as well as a range of spinal muscular atrophies and paraplegias. Other functional consequences could be the disruption of neuronal migration to the appropriate target layers or regions, as a consequence both of membrane

trafficking deficits and the disruption of the MTOC function of the GA and thus of cellular polarity [4]. Certain syndromes characterized by epilepsy or seizures could thus be a result of either the aberrant connectivity caused by such migration defects, or the defective transport of neurotransmitters or their receptors/inhibitors to the synapse. Additionally, the occurrence of central hypogonadism, dwarfism, obesity etc. of unknown etiology in certain POM Golgipathies could conceivably be due to deficits in neuroendocrine secretory activity controlling bodily hormonal homeostasis.

Cell cycle regulation:

Closely related to the structure and position of the GA is its role in the cell cycle. The typical ribbon structure of the GA in mammalian cells is usually localized close to the centrosome, a position regulated among others by a number of GA-associated proteins, including those involved in its structure and trafficking function (see for review [186]). During mitosis, the GA loses its pericentriolar position, as it does its ability to function as an independent MTOC, and undergoes fragmentation to yield small tubular-reticular structures and dispersed vesicles. While GA fragmentation could be considered a logical prerequisite for the partitioning of the GA into the daughter cells, it appears that GA fragmentation is in fact a prerequisite for mitosis itself, and blocking GA fragmentation, for example by blocking GRASP phosphorylation, acts as a "Golgi checkpoint" for the progression of mitosis [187-189]. Failure of the GA to fragment results in the failure of Aurora-A recruitment at the centrosome, essential for mitosis [190]. Several other GA proteins (for example GM130 and golgin-84) as well as non-GA proteins are also activated during fragmentation. In addition, a number of RAB GTPases including several GA-associated RABs, as well as the small G-protein ARF1 along with its activators and effectors, play essential roles at various steps of mitosis. Surprisingly, several GA proteins acquire new locations and functions during mitosis (reviewed in [188]). Some GA proteins, such as GM130, whose role in this regard has been described above, may

also play very specific roles in neurogenesis and neural progenitor division, by influencing cell polarity (reviewed in [191]) or the symmetry of mitosis, which plays a crucial role in the generation of different types of neuronal progenitors while still maintaining the pool of stem cells. For example, the asymmetric division of neural progenitor cells requires the interaction of the golgin GCP60 (also known as ACBD3 or PAP7) and Numb [192]. While the pathophysiological mechanisms underlying the syndromes characterized by macrocephaly mentioned above are not clear, most of the mutations detected result in a loss of function, and it is conceivable that uncontrolled proliferation or the dysregulation of the timing of symmetric versus asymmetric divisions during neurogenesis, could lead to the overproduction of certain neurons. In another instance of the overlap between the trafficking function of the GA and its role in neurogenesis, the *trans*-Golgi BIG2 protein encoded by *ARFGEF2*, essential for protein trafficking, is also involved in normal neural progenitor cell proliferation, migration and axonal growth in the developing mammalian cortex through its interaction with RAB11, another *trans*-Golgi protein. The early microcephaly and aberrant corticogenesis noted in ARPHN, caused by *ARFGEF2* mutations [59-62], could for example be due to defective neurogenesis and migration rather than defects in neuronal maturation or myelination.

It should not be forgotten that mutations in GA proteins whose function is essential early in neurodevelopment, for example during neurogenesis, might simply be embryonic lethal and thus pass unremarked.

Autophagy and apoptosis:

At the other end of the spectrum from cell proliferation and membrane expansion, the GA is also involved in normal or pathological cell death or the destruction of cellular contents. Both apoptosis and autophagy are normally occurring processes by which unwanted cells or cellular components are eliminated while limiting tissue damage (i.e. leakage of cellular contents). They occur during neurodevelopment, when the large excess of new neurons or

membranes produced is culled during the maturation of the CNS. In addition, they are also brought into play for the removal of damaged cells during conditions of stress or disease. In fact, the GA is increasingly thought to play a role in sensing stress and reestablishing cellular homeostasis; prolonged "Golgi stress", like ER stress, while not due to an intrinsic GA defect, nevertheless leads to impaired or abnormal GA function, contributing to pathogenesis and cell death, including by novel mechanisms other than apoptosis [193].

In autophagy, or more specifically, macroautophagy, cellular contents to be degraded are enveloped in a "phagophore" or "isolation membrane" and delivered to acidic lysosomes for destruction. There is evidence that the phagophore might bud directly from GA membranes, or alternatively, from the ER or ER-Golgi Intermediate Compartment [194,195]. The GA might additionally be directly involved in the degradation of undesirable cellular contents [196]. Several GA-associated RAB GTPases and their partners, normally involved in various stages of trafficking, also play key roles in the formation of the autophagosome [197-201], as do SNAREs, which are involved in autophagosome fusion (reviewed in [202]). Among other GA proteins, BECLIN1, a *trans*-Golgi protein involved in endosome-to-GA recycling, also plays a crucial early role in autophagosome formation (reviewed in [203]), by interacting with UVRAG, which normally mediates GA-to-ER retrograde transport by tethering COPI-coated vesicles but is displaced during autophagy [204]. Similarly, the *trans*-Golgi membrane-bound protein ATG9 is found in vesicles that contribute to autophagosome formation [199], and the regulation of its trafficking plays a crucial role in the induction of autophagy pathways [205,206]. Several coat adaptor proteins of the AP1, 2 and 4 classes are known to interact with ATG9, and are also necessary for autophagosome formation [207,208].

Apoptosis, resulting from mitochondrial membrane permeabilization in response to internal or external signals and leading cell death by strictly regulated molecular and cellular mechanisms, is mediated by members of the caspase and BCL-2 families of proteins. Much of

the evidence for the involvement of GA proteins in apoptosis comes from neurodegenerative disorders such as Alzheimer, Parkinson and Huntington Diseases, where the GA undergoes stress due to an accumulation of aberrant and misfolded proteins or peptides, also causing it to fragment (reviewed in [209-211]). However, some of the early machinery for apoptosis localize to the GA, and is involved in cleaving various GA proteins that also play a role in neurodevelopment (for example GRASP65, GM130 or GIANTIN). Their cleavage triggers the mitosis-like disassembly of the GA and subsequent apoptosis (reviewed in [212]). Some GA proteins also have a larger signal transduction role – GMAP210 and golgin-160 as well as cleaved p115 fragments are translocated to the nucleus during apoptosis, triggering further apoptotic changes [213,214]. It is certainly possible that mutations that interfere with the cleavage of such GA proteins or that lead to the production of truncated proteins would either curtail or augment apoptosis, with consequences for neurodevelopment ranging from insufficient neurogenesis to excess neurons that are not culled and that lead to macrocephaly, aberrant connectivity and related disorders.

Biosynthesis and processing of lipids and proteins:

As mentioned previously, the GA is also intimately involved in the post-translational modification of proteins and the biosynthesis of some lipids. In terms of the physiological effects of mutations in these proteins versus mutations in proteins involved in trafficking per se, there might be a convergence, since the functional consequences of the lack of delivery of a modified protein to its target intracellular compartment and the lack of its modification in the first place are likely to be similar in at least some respects. In addition, the highly specialized nature of the nervous system implies a corresponding adaptation of GA trafficking function in the component cells (for example, the occurrence of Golgi outposts in dendrites), and correspondingly, defects in GA enzyme function often lead to neurological consequences (also reviewed in [2,4]). A prime example of this convergence is provided by the CDGs, which could

be related to structural/mechanical deficits (e.g. due to the mutation of COG subunits necessary for vesicle tethering) or due to enzymatic deficits (due to the failure of glycosylation).

Conclusion

While the large number of neurodevelopmental Golgipathies described in this review contain some surprises, it appears as if the majority were, and are, simply hiding in plain sight. The GA is involved in a very large range of functions spanning every stage of a cell's lifespan; an even larger number of overlapping GA-associated proteins and pathways carry out or regulate these functions. It is therefore to be expected that as our knowledge of these proteins and pathways grows, and as modern sequencing methods provide a molecular diagnosis for more obscure syndromes, the range of phenotypes that we know to be caused by defective GA proteins and their partners will expand. This is especially true when one considers the essential roles played by the GA in the formation, growth and maturation of the brain and nervous system. In fact, the spectrum of syndromes in which mutations in GA-associated proteins are implicated, and the overlap in the cellular roles played by these proteins, evoke the intriguing idea that the GA might modify its role in keeping with the needs of the cell or the organism during its lifespan. For instance, the same proteins that are actively involved in cell cycle initiation or regulation during neurogenesis, when abundant proliferation is required, might be repurposed to lend a hand in neuronal migration, apoptosis or maturation, meet secretory trafficking needs during synaptogenesis and myelination as well as normal cellular function for the major part of the lifespan of the cell, and finally play a role in repair and damage control during aging (see also [215]). From this perspective, this vast array of neurodevelopmental Golgipathies appears not as isolated syndromes that differ from each other, but as points that fall along a few key functional continua, with flexible phenotypes that primarily reflect the

developmental stage at which function is interrupted or altered. Such an organelle-centric approach might eventually make it easier to understand the pathophysiology of these disorders.

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Conflict of Interest

The authors declare no conflicts of interest

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TABLE 1. Golgipathies associated with Postnatal-Onset Microcephaly

Disease/Syndrome	# MIM	Mode of Inheritance	GA protein	Major neurological signs
Dyggve-Melchior-Clausen syndrome (DMC)	223800	AR	DYMECLIN	POM, ID, thin corpus callosum
Warburg-Micro syndrome (WARBM1-4)	600118 614225 614222 615663	AR AR AR AR	RAB3GAP1 RAB3GAP2 RAB18 TBC1D20	POM, ID, progressive limb spasticity, peripheral axonal neuropathy, visual impairment, thin corpus callosum
Neurodevelopmental Disorder with Microcephaly, Epilepsy, Brain Atrophy (NEDMEBA)	617862	AR	TRAPPC6B	POM, ID, hypotonia, hand tremors, seizures
Autosomal Recessive Mental Retardation 13 (MRT13)	613192	AR	TRAPPC9	POM, ID, thin corpus callosum
Progressive Childhood Encephalopathy (PEBAS)	617669	AR	TRAPPC12	POM or PM, truncal hypotonia with appendicular spasticity, visual impairment, partial agenesis of the corpus callosum
Autosomal Recessive Mental Retardation 61 (MRT61)	617773	AR	IPORIN	POM, ID, thin corpus callosum
Autosomal Dominant Mental Retardation 34 (MRD34)	616351	AD	COL4A3BP	POM, ID, visual impairment, seizures
Cohen syndrome (COH)	216550	AR	VPS13B	POM, ID, visual impairment, short and thick corpus callosum
Pontocerebellar Hypoplasia Type 2E (PCH2E)	615851	AR	VPS53	POM, pontocerebellar hypoplasia, progressive spasticity, seizures, thin corpus callosum
Pontocerebellar Hypoplasia Type 11 (PCH11)	617695	AR	TBC1D23	POM, ID, pontocerebellar hypoplasia, thin corpus callosum
Autosomal Recessive Periventricular Heterotopia with Microcephaly (ARPHM)	608097	AR	BIG2	POM, ID, periventricular heterotopia, seizures, thin corpus callosum
POM-associated Congenital Disorders of Glycosylation (CDG types 2C, 2E, 2F, 2G, 2H, 2I, 2J, 2K, 2M, 2Q, SHNS, AMRS)	611209 617395 613489 613612 615328 608779 611182 603585 300896 615553 266265 614727	AR AR AR AR AR AR AR AR XLD AR AR AR	COG1 COG2 COG4 COG5 COG6 COG7 COG8 SLC35A1 SLC35A2 SLC35A3 SLC35C1 TMEM165	POM, ID, multiple and variable neurological manifestations
Mental Retardation, Enteropathy, Deafness, Peripheral Neuropathy, Ichthyosis, Keratoderma (MEDNIK)	609313	AR	AP1S1	POM, ID, peripheral neuropathy
Takenouchi-Kosaki syndrome (TKS)	616737	AD	CDC42	POM or PM, ID, seizures, visual impairments, thin corpus callosum
Neuromuscular syndrome with Microcephaly	602580*	AR	GM130	POM, central hypotonia, thin corpus callosum
Novel Pontocerebellar Hypoplasia	NA	AR	VPS51	POM, ID, pontocerebellar hypoplasia, visual impairment, thin corpus callosum

AR=Autosomal Recessive, AD=Autosomal Dominant, XLD=X-linked Dominant
*OMIM reference corresponds to the gene instead of the disease.

TABLE 2.

Golgipathies associated with Primary or Unknown-onset Microcephaly or Macrocephaly

Disease/Syndrome	# MIM	Mode of Inheritance	GA protein	Major neurological signs
Autosomal Recessive Primary Microcephaly type 2 (MCPH2)	604317	AR	WDR62	PM, ID, seizures
Autosomal Recessive Primary Microcephaly type 3 (MCPH3)	604804	AR	CDK5RAP2	PM, ID
Limb Girdle Muscular Dystrophy (LGMDR18)	615356	AR	TRAPPC11	Microcephaly of unknown onset, ID, limb spasticity, seizures, ataxia, visual impairments
Autosomal Dominant Microcephalic dwarfism with micrognathia (SRMMD)	617164	AD	COPD	PM, ID, mild cerebellar atrophy, visual impairments, thin corpus callosum
Autosomal Recessive Primary Microcephaly type 19 (MCPH19)	617800	AR	COPB2	PM, ID, spasticity, visual impairments, thin corpus callosum
Progressive Encephalopathy with Edema, Hypsarrythmia and Optic Atrophy-like syndrome (PEHOL)	617507	AR	GIRDIN	PM, ID, severe encephalopathy, seizures, hypotonia, peripheral hypertonia with spasticity, visual impairments, thin corpus callosum
AP4-deficiency Syndrome	613744 612936 614066 614067	AR AR AR AR	AP4E1 AP4M1 AP4B1 AP4S1	PM, ID Spastic paraplegia Neonatal hypotonia
Hermansky-Pudlak syndrome (HPS2)	608233	AR	AP3B1	Microcephaly of unknown onset, ID
Christianson Syndrome (MRXSCH)	300243	XLD	SLC9A6	PM or Microcephaly of unknown onset, ID, seizures, visual impairments
Pettigrew syndrome (PGS)	304340	XLR	AP1S2	Microcephaly of unknown onset, ID, seizures, Dandy-Walker malformation
Early Infantile Epileptic Encephalopathy (EIEE49)	617281	AR	DENND5A	Microcephaly of unknown onset, ID, spastic tetraplegia, seizures, visual impairment, corpus callosum dysgenesis
X-linked form of ID (MRX72) **Waisman syndrome (WSMN)**	300271 311510	XLR XLR	RAB39B RAB39B	Macrocephaly ID Early onset Parkinsonism
Macrocephaly, Dysmorphic Facies and Psychomotor Retardation (MDFPMR)	617011	AR	HERC1	Macrocephaly, ID, seizures, hypotonia, ataxia
Polyhydramnios, Megalencephaly and Symptomatic Epilepsy (PMSE)	611087	AR	STRADA	Macrocephaly, ID, seizures, hypotonia
Autosomal Dominant Mental Retardation (MRD48)	617751	AD	RAC1	Microcephaly of unknown onset or macrocephaly, ID, seizures, thin corpus callosum

AR=Autosomal Recessive, AD=Autosomal Dominant, XLD=X-linked Dominant, XLR=X-linked Recessive

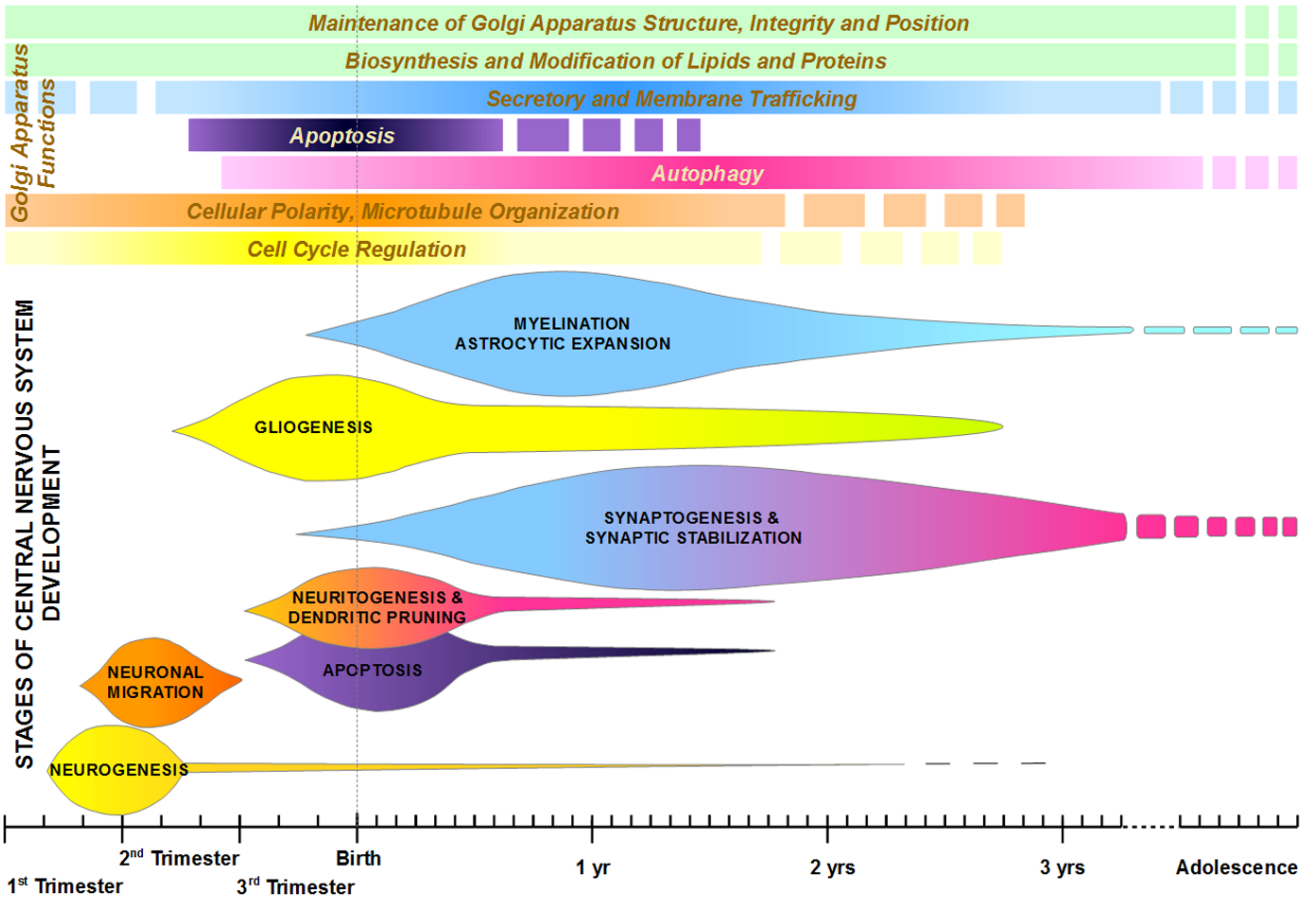
TABLE 3. Neurodevelopmental Golgipathies without Microcephaly

Disease/Syndrome	# MIM	Mode of Inheritance	GA protein	Major neurological signs
Non-syndromic form of ID (MRX41)	300849	XLD	GDI1	ID of variable severity
Periventricular Nodular Heterotopia (PVNH1)	300049	XLD	FLNA	ID in males Epilepsy
Schuurs-Hoeijmakers syndrome (SHMS)	615009	AD	PACS1	ID with remarkable similarity in facial features
Autosomal Rcessive Spinocerebellar Ataxia (SCAR21)	616719	AR	SCYL1	ID, Cerebellar atrophy; peripheral neuropathy
Autosomal Dominant Spinal Muscular Atrophy (SMALED2)	615290	AD	BICAUDAL	Spasticity
Autosomal Recessive spastic Ataxia (SPAX2)	611302	AR	KIF1C	Cerebellar ataxia Atrophy of the corpus callosum
Metabolic Encephalomyopathic Crises, Recurrent with Rhabdomyolysis, Cardiac Arrythmias and Neurodegeneration (MECRCN)	616878	AR	TANGO2	Muscle weakness, ataxia, seizures
Progressive Myoclonic Epilepsy (EPM6)	614018	AR	GOSR2	Progressive ataxia Seizures
Neuropathy Hereditary Sensory and Autonomic type IIB (HSAN2B)	613115	AR	FAM134B	Childhood onset autonomic neuropathy, sensory deficits, loss of myelinating fibers
Deafness Autosomal Dominant 67 (DFNA67)	616340	AD	OSBPL2	Sensorineural hearing loss
Hermansky-Pudlak syndrome (HSP10)	617050	AR	AP3D1	Epilepsy Neurodevelopmental delay Intractable myoclonic seizures

AR=Autosomal Recessive, AD=Autosomal Dominant, XLD=X-linked Dominant

Legend to Figure 1: Temporal relationship between major stages of central nervous system development and various physiological functions of the Golgi apparatus

Schematic representation summarizing some of the physiological functions of the Golgi apparatus (GA) proteins (upper section) and major developmental processes of the central nervous system in which these proteins are involved during embryonic/fetal and postnatal life (lower section). Proteins involved in the maintenance of GA structure, integrity and position are required throughout life, as are those involved in the biosynthesis and modification of certain lipids and most proteins. However, the need for other GA functions increases periodically, and proteins involved in these functions may not play a role throughout life or may switch to other roles depending on the stage of the lifespan. For example, during neurogenesis and gliogenesis, when mitotic activity predominates, GA proteins involved in cell cycle regulation (yellow) would be expected to play a major role, and defects in these proteins would have maximum impact and lead to disorders reflecting a lack of neurons and glia. At later stages, other functions predominate, such as cellular polarity and microtubule organization (orange; particularly important for migration and morphogenesis, including the establishment and maturation of the axon and dendritic arbor), apoptosis (violet; crucial for the programmed death of the large excess of neurons produced), autophagy (pink; necessary to remodel the cell but also important in maintenance and repair throughout the lifespan, when it is involved in neurodegenerative processes) and secretory and membrane trafficking (blue; essential for the huge expansion of the cell membrane and secretory activity during synaptogenesis in neurons, branching of astrocytes and myelination by oligodendrocytes, but also necessary for neuronal and glial function throughout the lifespan). NB: the timeline of some of the processes described, for example neurogenesis and myelination, is still subject to debate; some processes involve two or more GA functions simultaneously.


Golgi Apparatus Functions
Maintenance of Golgi Apparatus Structure, Integrity and Position
Biosynthesis and Modification of Lipids and Proteins
Secretory and Membrane Trafficking
Apoptosis
Autophagy
Cellular Polarity, Microtubule Organization
Cell Cycle Regulation
STAGES OF CENTRAL NERVOUS SYSTEM DEVELOPMENT
MYELINATION
ASTROCYTIC EXPANSION
GLIOGENESIS
SYNAPTOGENESIS &
SYNAPTIC STABILIZATION
NEURITOGENESIS &
DENDRITIC PRUNING
APOPTOSIS
NEURONAL MIGRATION
NEUROGENESIS
1st Trimester
2nd Trimester
3rd Trimester
Birth
1 yr
2 yrs
3 yrs
Adolescence